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(71) Applicant(s)
Hiran Asoka Malinga Ratwatte
(Incorporated in the United Kingdom)
35 Gainsborough Drive, ASCOT, Berkshire, SL5 8TA, United Kingdom

(72) Inventor(s)
Hiran Asoka Malinga Ratwatte

(74) Agent and/or Address for Service
Hiran Asoka Malinga Ratwatte
35 Gainsborough Drive, ASCOT, Berkshire, SL5 8TA, United Kingdom

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(54) Abstract Title
A method of forming dose units of active agents

(57) A method of producing agent forms by dispersing an agent composition in a solution of a coating material in a liquid carrier material and spraying the resultant dispersed mixture to form fine droplets which are frozen. Drying the said frozen particles to produce a plurality of individual solid particles comprising of the agent composition coated with the coating material. The coated particles have sustained release properties of the agent and the method is useful for producing sustained release unit dose delivery systems of process sensitive materials such as bio-pharmaceuticals, as well as other agents such as vitamins.

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The claims were filed later than the filing date within the period prescribed by Rule 25(1) of the Patents Rules 1995.

METHOD OF FORMING DOSE UNITS OF ACTIVE AGENTS

The present invention relates to vehicles for the delivery of agents to the human or animal body. Specifically the invention relates to the formation of particles containing active agent, and further relates to a method of coating such particles.

Recently there has been an expansion in the number and type of delivery systems available for delivering drugs or other agents. Liquid injection and tablets have been known for hundreds of years. In more recent times alternative drug delivery systems have increasingly come to the fore. These include capsules, powder inhalations, parenteral delivery systems such as injectable forms which are sterile and filled into sealed ampoules or vials, transdermal delivery devices and trans-mucous membrane systems such as anal or vaginal suppositories.

More recently drug delivery devices have been developed which permit the controlled and sustained or intermittent release of drugs into biological systems.

It has now been discovered however that many conventional methods of production are frequently not suitable for producing delivery units containing agents which are

physically or chemically unstable or heat sensitive. This particularly applies to the bio-pharmaceuticals that are arising from the emerging bio-technology industry.

For example, one conventional process is spray drying. This makes use of high temperature drying steps involving the use of chemically aggressive organic solvents. Both the temperature and solvents can be deleterious to the properties of unstable active agents.

It is an object of the present invention to provide a new method for processing agents into a form acceptable for delivery to biological systems, which method is capable of application, inter alia, with unstable drugs and other agents.

It is a particular object of the present invention to provide a low temperature process for the production of particulate dose forms comprising agent.

According one aspect of the present invention there is provided a method of producing agent forms, which method comprises: providing an agent composition, contacting said composition with a liquid carrier material, spraying the resultant mixture to form droplets thereof, freezing said droplets to produce frozen particles, and fre z

drying said particles, thereby to produce a plurality of solid particles comprising the agent composition.

In this way agent forms may be produced from a loose starting composition at a low temperature and without the need for solvent/heat treatment. Thus chemically, physically or temperature unstable agents may be formed into a suitable form for incorporation into an gent delivery device without fear of damaging the agent by the processing method.

In the contacting step, the agent composition and carrier liquid material may form an emulsion of liquid agent dispersed in the carrier liquid. In this case the freeze dried particles may comprise agent coated in carrier material.

Alternatively the agent composition may form a suspension of solid or semi-solid agent, such as gel, dispersed in the liquid carrier material. In this case the freeze dried particles may comprise agent coated in carrier material.

Alternatively the agent composition may be dissolved in the carrier liquid to form a solution of agent in the liquid carrier material. In this case the freeze dried

particles may comprise an homogenous mixture of agent and carrier.

The foregoing alternatives are not mutually exclusive, and depending upon the nature of the agent composition, the resultant mixture may be made up one or more of each alternative.

The agent composition may comprise an active agent or agents per se. Alternatively, the composition may comprise an active agent or agents along one or more excipients or additives.

The agent composition may comprise an agent absorbed into another element such as a polymer. Suitable elements include polyacrylamides, agar, lipids, proteins, carbohydrates and the like.

The agent may comprises a long chain molecule such as a polymer.

The agent may comprises a liposome which forms a suspension in the carrier liquid.

Other agent compositions include small tablets, or other small particles which are mixed to form a dispersion in

the carri r liquid.

For example, in one embodiment the agent composition comprises a crystalline powder of the agent.

The agent may comprise a drug or other pharmaceutically active substance, such as a peptide, an oligopeptide, a protein, a hormone, a nucleic acid, a polysaccharide, a peptide with polysaccharide side chains, a lipid, a lipopolysaccharide, a vaccine, a vitamin.

Excipients which may be included in the agent composition may comprise one or more of mannitol, microcrystalline cellulose, flavouring, preservative, surfactant.

The agent composition may comprise a food flavouring, and the food flavouring particles formed in the method may be incorporated into a foodstuff.

The method of the present invention is particularly useful for forming agent forms comprising delicate agents. Hence the agent may comprise biological material, for example a micro-organism such as a useful bacteria or a virus.

In particular the agent may comprise a genetically

engineered virus for therapeutic or oth r useful application.

The agent composition may comprise an agent form produced according to the method as hereinbefore described, which agent form is contacted with the carrier liquid to form a dispersion therein. The agent form is thereby coated in carrier material by the method of the present invention. The process may be repeated to produce multiple coating layers, of the same or different compositions of carrier material.

Where an agent would tend to dissolve in the carrier liquid it may be included in a stabilising formulation which substantially prevents dissolution thereof in the carrier liquid material. In this way agents which would normally dissolve in the carrier liquid may be coated with carrier material. By way of example the stabilising composition may comprise one or more of a carbohydrate, a lipid, a lipopolysaccharide, a protein, a surfactant.

The carrier liquid material may comprises water. Frozen water (ice) will be removed during the freeze drying process. Water has the advantage when present in the carrier liquid material of requiring only a small degree of cooling from ambient temperature, say 20 degrees

centigrade, to below the freezing point; 0 degrees centigrade. Hence little energy is required to produce the required cooling in the freeze drying and spray cooling steps.

The carrier material may comprise a polymer. The carrier material may comprise one or more of gelatine, carageenan, alginate, carbopol, carboxymethyl cellulose, or ethyl cellulose. The polymer may be rendered liquid and/or sprayable by the addition of water or another suitable solvent or liquid removable by freeze drying.

The spraying step preferably forms an aerosol of droplets, thereby facilitating the freezing of the droplets while still airborne.

The droplets may be cooled by contacting said droplets with a gas cooled to below the freezing point of the mixture. Preferably cooling is effected by contacting said droplets with a stream of cooled gas. The droplets may freeze as frozen droplets, or flakes or other shapes depending upon the nature of the material frozen and the conditions of freezing. The cooled particles may be stored in a chilled enviroment and mixed with other substances as desired, or otherwise treated when chilled. Subsequently the particles may be freeze dried to render

the particles stable at room temperatur .

The freeze drying may be by one of the known methods of which the person skilled in the art will be capable of carrying out. Typically freeze drying involves sublimation of the frozen "liquid" in a vacuum.

In another aspect of the invention the method may comprise storing the frozen droplets in a chilled environment prior to freeze drying.

In yet another aspect of the invention the frozen droplets may be mixed with a composition for tablet manufacture and tabletted by compression before freeze drying.

In a further aspect of the invention the method is adapted to produce particles of between about a micron and about a thousand microns. The temperature to which the gas is cooled may be chosen to produce a desired droplet size. Alternatively, or in addition, the spray droplets may be formed by an adjustable spray nozzle, adjustment of which nozzle permits variation of the droplet size.

In another aspect of the invention, ther is provided a

method of coating agent forms comprising spraying a liquid carrier material as hereinbefore described onto a plurality of agent forms, and cooling said sprayed agent forms to solidify the carrier material, and freeze drying the resultant particles to leave an agent form coated in carrier material.

The agent forms coated may be coated as freeze dried particles, or as solidified droplets formed before freeze drying.

The coating preferably fully encapsulates the agent forms, but partial coating may occur in certain embodiments.

The coating procedure may be repeated on the coated agent forms to build up multi-layer coatings. The coatings may comprise the same coating material or different coating materials. Agents may be included in the carrier liquid to produce one or more agent containing layers.

The coating layers and/or agent forms produced by the present invention may rendered porous after freeze drying, the pores corresponding to the sublimed matter.

Following is a description by way of example only of

examples demonstrating application of the present invention.

Example 1

A bio-pharmaceutical which has a relatively low solubility is chosen to be coated. A coating solution of a carrier polymer, such as gelatine, in water is formed. To this solution is added crystalline powdered drug, and mixed to form a uniform suspension of drug crystals in the solution. The liquid mixture thereby formed is then sprayed from a nozzle by means of compressed air into which the suspension is entrained as droplets. The droplets disperse from the nozzle to form an aerosol. The nozzle is sprayed into a moving stream of air cooled to well below the freezing point of the liquid mixture. The frozen, solidified droplets are then collected as they fall under the influence of gravity. The droplets are maintained in a cool atmosphere until it is desired to freeze dry the frozen droplets. Freeze drying is carried out by the known methods to remove the ice from the droplets, leaving solid particles of drug crystals coated in porous polymeric gelatine. The pores correspond to previous disposition of the removed ice.

The solid particles are then incorporated into a drug

delivery device, for example a capsule, and may then be administered to a patient. The polymeric coating layer provides a protective coating, which also serves to control the rate at which agent is dissolved into a system to which the capsule is administered. The control function may be altered by changing the coating thickness, and by varying the fraction of solvent (water) in the liquid mixture before spraying. If it is desired to produce multiple coatings, then the procedure can be repeated, this time substituting the particles to be re-coated for the drug crystals.

Example 2

A bio-pharmaceutical is chosen which is relatively soluble in water, to the extent that it dissolves almost immediately on contact therewith at room temperature. A stabilizing formulation is formed consisting of water and a carbohydrate and surfactant. The drug is added to the stabilising formulation to form a mixture. The mixture thereby formed is then sprayed from a nozzle by means of compressed air into which the mixture is entrained as droplets. The droplets disperse from the nozzle of a spray gun to form an aerosol. The nozzle is sprayed into a moving stream of air cooled to well below the freezing point of the mixture. The frozen, solidified droplets are

then collected as they fall under the influence of gravity. The droplets are maintained in a cool atmosphere until it is desired to freeze dry the frozen droplets. Freeze drying is carried out by the known methods to remove the ice from the droplets, leaving particles consisting of an homogeneous mixture of drug and stabilising formulation. The agent form can be now be coated in the same way as the drug crystals were coated in example one, either before freeze drying, or after freeze drying.

The present invention provides a low temperature method of forming particulate drug forms from a wide range of starting points. Solid drug compositions can be formed without the need for damaging solvent processing or high temperatures. The method allows the production of multi-layer particles, the layers of which can consist of flavourings, drugs, excipients as required.

CLAIMS

1. A method of producing agent forms, which method comprises: providing an agent composition comprising an agent, dispersing said agent composition in a solution of a coating material in a liquid carrier material, spraying the resultant dispersed mixture to form droplets thereof, freezing said droplets to produce frozen particles and drying said particles, thereby to produce a plurality of solid, individual particles comprising the agent composition coated with said coating material.

2. A method as claimed in claim 1, wherein said agent composition comprises a carrier for said agent.

3. A method as claimed in claim 2, wherein said carrier comprises a polymer, such for example as polyacrylamide, agar, lipid, protein or carbohydrate, which polymer is adapted to absorb said agent.

4. A method as claimed in claim 2, wherein said carrier comprises a liposome which carries said agent.

5. A method as claimed in any preceding claim, wherein said agent comprises a drug.

6. A method as claimed in any preceding claim, wherein said agent comprises a pharmaceutically active substance, such, for example, as a peptide, an oligopeptide, a protein, a hormone, a nucleic acid, a polysaccharide, a peptide with polysaccharide side chains, a lipid, a lipopolysaccharide, a vaccine, or a vitamin.

7. A method as claimed in any preceding claim, wherein said agent comprises biological material such as a micro-organism such as a useful bacterial strain or a virus.

8. A method as claimed in any preceding claim, wherein said agent composition further comprises one or more excipients or additives.

9. A method as claimed in any preceding claim, wherein said agent composition further comprises a stabilising agent for preventing said agent from dissolving when contacted by said liquid carrier material.

10. A method as claimed in claim 12, which stabilising agent comprises one or more of a carbohydrate, a lipid, a lipopolysaccharide, a protein, and a surfactant.

11. A method as claimed in any preceding claim,

characterised in that said dispersed mixture is viscous.

12. A method as claimed in any preceding claim, wherein said liquid carrier material comprises water.

13. A method as claimed in any preceding claim, wherein said coating material comprises a polymer.

14. A method as claimed in claim 13, wherein said polymer is selected from one or more of gelatine, carageenan, alginate, carbopol, carboxymethyl cellulose, and ethyl cellulose.

15. A method as claimed in any preceding claim, wherein said drying of the particles comprises freeze-drying.

16. A method as claimed in claim 15, wherein said frozen particles are mixed with a composition for tablet manufacture and tabletted by compression prior to being freeze-dried.

17. Apparatus for producing agent forms in accordance with the method of any preceding claim, which apparatus comprises dispersing means for dispersing an agent composition comprising an agent in a solution of coating

material in a liquid carrier material, spraying means for spraying the resultant dispersed mixture to form droplets thereof, freezing means for freezing said droplets to produce frozen particles and drying means for drying said frozen particles, thereby to produce a plurality of solid, individual particles of said agent composition coated with said coating material.

18. An agent form comprising a plurality of dried particles of an agent composition, which agent form is produced in accordance with the method of any of claims 1 - 16.

19. An agent form as claimed in claim 18, which agent form comprises a drug composition for administration to a patient.

20. An agent form as claimed in claim 19, wherein said particulate drug composition comprises a plurality of particles comprising drug crystals coated in one or more layers of a coating material, which drug crystals are adapted to be released through said one or more layers of coating material over a sustained period of time.

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Application No: GB 9719457.5
Claims searched: 1-20

Examiner: Jason Bellia
Date of search: 4 December 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P):

Int Cl (Ed.6): A61K 9/16, 9/19, 9/50

Other: ONLINE: EPODOC, WPI, PAJ

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	GB 1 316 522	(DU PONT) See page 1 line 38-75, page 2 line 3-27, page 3 line 32-48 & Examples	1-3, 6, 8, 13, 15 & 18
X	EP 0 668 013 A2	(NIPPON TELELGRAPH) See page 4 line 14-31, page 4 line 52-page 5 line 17	1-3, 7-8, 11-13, 15 & 18
X	EP 0413 865 A1	(TAISHO) See page 2 line 32 - page 4 line 36 & page 7 line 23-26	1-3, 5-16, 18 & 19
X	EP 0 081 913 A1	(WYETH) See page 5 line 13 - page 8 line 7	1-3, 5, 6, 8-15, 17 & 19
X	WO 88/10150 A1	(GLATT MASCHINEN) See page 16 line 8-20 & claims 1 & 2 and also EPODOC/WPI abstract	1-3, 5, 6, 8, 11-15, 18 & 19
X	US 5 656 597	(SKRABANJA) See column 1line 34-43 & Examples	1-3, 6, 8, 12, 13, 15 & 18

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

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Application No: GB 9719457.5
Claims searched: 1-20

Examiner: Jason Bellia
Date of search: 4 December 1998

Category	Identity of document and relevant passage		Relevant to claims
X	US 5 611 973	(GURFEIN) See column 2 line 19, column 3line 15-62	1-3, 5, 6, 8-15, 18 & 19

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Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.